REMARKS

These remarks are in response to the Office Action mailed April 22, 2008. Claims 49 and 57 have been amended. Support for the amendments can be found throughout the specification and claims as originally filed (see, *e.g.*, claims 2-4 as originally filed). Claim 59 has been cancelled without prejudice to Applicants' right to prosecute the cancelled subject matter in any divisional, continuation, continuation-in-part or other application. No new matter is believed to have been introduced.

I. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 49, 51-55, 57-64, 79, 81-88 and 96-97 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The claims allegedly contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner spends several pages describing the nature of the claimed invention. At page 5 of the Office Action, the Examiner indicates, "The invention is complex in that it involves measuring a change in the level of RNA by amplification..." Applicants respectfully submit that techniques including quantitative PCR, digital PCR and the like are routinely performed in the art to measure expression levels with a high degree of accuracy and the level of skill in this area is high. In fact, an overwhelming number of treatises, journals, and patent documents discuss such techniques. Thus, Applicants disagree with characterizing measuring a change in the level of RNA by amplification as "complex". Applicants have provided a description of PCR and RT-PCR sufficient to provide enablement for quantifying expression levels of RNA in a sample, particularly in view of the high level of skill in this area and automated techniques.

The Office Action further indicates that the claims are directed to "any biological sample" and "any control" and the use in "any therapeutic intervention" (see, *e.g.*, page 5, 3rd paragraph of the Office Action). Applicants have amended the claims to more clearly set forth the invention. Applicants have amended the claims to recite a "colorectal sample". Applicants respectfully submit that one of ordinary

skill in the relevant art is capable of defining a control population/sample for purposes of the disclosure. For example, it appears that the Office Action believes that any control is appropriate; however, one of skill in the art measuring expression levels of a biomarker from a potential disease population would know to measure and compare the expression level of a corresponding biomarker in a normal control sample. However, to further clarify what is already recognized to those of skill in the art, Applicants have amended claim 49 to more clearly set forth the invention.

The Office Action further alleges that the specification fails to teach how the measurement of RNA expression can be used to manage patient care. Applicants respectfully submit that the claims and specification provide that a difference in a biomarker expression level compared to a control "identifies the subject as a candidate for the management of colorectal cancer. . . ." (see, *e.g.*, claim 57). In other words if there is aberrant expression levels the subject should be further monitored, tested, screened or otherwise "managed" for risks of colorectal cancer or polyps. Applicants believe that the claims and the specification sufficiently describe and enable such "identification".

The Office Action further misconstrues that statements at page 7, paragraph 23 of the specification (discussed also at page 8, lines 1-5 of the Office Action). Applicants respectfully submit that the reference to "protein expression" levels made in the Office Action appears to misstate the claimed invention, which recites measuring expression/transcription levels. More particular, the Office cites to Chen alleging, ". . .it is not possible to predict overall protein expression levels based upon average mRNA abundance in lung cancer samples." Applicants submit it is recognized that mRNA can be expressed but not translated to protein due to post transcriptional regulation; however, this does not negate the importance of measuring transcriptional expression levels. The mere fact that such gene expression is "turned on" has physiological relevance and molecular significance.

The Office further cites to Lucentini *et al.* for the position that follow on studies show that gene association studies are "typically wrong". However, Applicants submit that data obtained and published in peer reviewed journals support Applicants' claimed invention post-filing (see, *e.g.*, Hao, *et al.*, Clin Cancer Res. 2005 Feb 15;11(4):1400-7) and further follow on studies, the data of which was provided in

Dr. Nancy Lee's 1.132 Declaration (submitted previously), support the claimed invention. It appears that the PTO is requiring full clinical trial data to support the claimed invention, when all that is required is that the claimed invention be reasonably supported and that the data have correlation to the claimed invention. The Examiner will recognize that to date the follow on studies have supported the claimed invention, and although additional follow on studies are on-going, it is not the place of the PTO to require the same data necessary for FDA submissions. Furthermore, patent protection for the claimed invention provides the necessary limited period of exclusivity in order to justify the expense associate with clinical trials. Applicants respectfully submit that the claims are supported by the specification as filed, correlate to the data obtained and demonstrated to the Office. Applicants have demonstrated both in the specification and the declaration by Dr. Lee, that (i) measuring expression levels of the at least two polynucleotides in colorectal samples is associated with colorectal cancer or polyps (including the markers of SEQ ID NO:1, 2 and 5), (ii) that other markers ("comprising") can also be used in addition to the recited at least two markers (i.e., 3, 4, 5, 6, or more other biomarkers), and that (iii) the technique for measuring RNA expression are useful in the methods of the disclosure.

Furthermore, the Office Action alleges (citing to Wagner *et al.*) that biomarkers require validation (see, pg. 11, line 1). Applicants respectfully submit that additional subjects have been used in further validation studies (see, 1.132 Declaration by Dr. Lee). It is important to recognize that a separate and distinct governmental agency, The Food & Drug Administration, regulates clinical testing processes. The question for the PTO is whether the inventive concept is satisfied by the specification and claims. Applicants respectfully submit that the specification teaches and enables measuring a panel of biomarkers, quantifying expression and comparing the values to a control, wherein a change is indicative of a colorectal cancer or colorectal polyps. This is the subject matter described and claimed by the specification. It appears that the Office is yet asking for more data in addition to (i) the animal model data of the specification, in addition to (ii) the colorectal cancer patient data of the specification, and in addition to (iii) the 92 normal subject, 148 subjects with family history/self history, 100 patients with polyps and the at least 50

patients with cancer as set forth in the 1.132 Declaration, all of which demonstrate the claimed invention.

Applicants submit that the claimed invention is fully supported by the specification as filed in view of the level of ordinary skill in the art. For example, methods of quantifying RNA levels are known in the art and described in the specification. Comparing expression levels to normal controls is described by the specification. Identifying difference is expression levels to identify subjects at risk for colorectal disease or disorders are described by the specification. The Examiner is respectfully reminded that the test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.,* 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 188 USPQ 659 (CCPA 1976); MPEP §2164.01. The amount of experimentation that is permissible to provide enablement depends upon a number of factors, which include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims. *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988); MPEP §2164.01.

The Office Action states, "The specification discloses a single panel of genes exhibiting altered expression in a mouse model comprising a chemically induced mutation in the PC gene and normal control littermates for which there was not aberration of the APC gene and analysis of a panel of six biomarkers applied to samples from patients known to have CRC and from normal controls. The application also discloses differences in expression of three biomarkers in biopsy samples taken from one exemplary patient diagnosed with CRC." (see, *e.g.*, page 14-15 of the Office Action). The Office Action then goes on to allege that "there would be a large and prohibitive amount of experimentation required to make and use the claimed invention." (See, page 17, lines 1-3 of the Office Action). Applicants respectfully disagree and submit that any experimentation, if needed (which it is not), would not be undue. This is particularly true in light of the specification, the ordinary

skill in the art (which is high, see page 14, lines 16-17 of the office action) and the demonstrated success and confirmation of the methods of the disclosure in Dr. Lee's 1.132 Declaration.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. "The quality of any necessary experimentation would clearly be undue when "ingenuity beyond that to be expected of one of ordinary skill in the art" is required. *Fields v. Conover,* 443 F.2d 1386, 1391, 170 USPQ 276, 279 (1971). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. . . ." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (*citing, In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). Here, any additional experimentation would be merely routine (*e.g.*, quantifying additional data points using the methods and markers described herein) and would not require additional "ingenuity". Applicants submit that such data was provided in the 1.132 Declaration of Dr. Lee. The Office Action also appears to question the quantity of specific examples. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. So long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of Section 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Here Applicants have provided a number of examples including animal models and human subject data including the 92 normal subject, 148 subjects with family history/self history, 100 patients with polyps and the at least 50 patients with cancer as set forth in the 1.132 Declaration, all of which demonstrate the claimed invention.

The Office Action states at page 21, that the claims encompass measuring expression of SEQ ID NO:1, 2 or 5 and "comprises" additional undefined sequences. Applicants respectfully submit that the data of record demonstrates that the foregoing specific biomarkers can be used in assessing colorectal cancer and polyps. Furthermore, the data demonstrate that additional markers can be used (see

e.g., the data in the Declaration by Dr. Lee and the specification as originally filed) including those comprising SEQ ID NO:3, 4, and 6-22.

It appears that the majority of the rejection is directed to the claims not reciting measurement of the biomarkers and the type of sample used. Applicants believe that the foregoing remarks and amendments address the rejection. For at least the foregoing reasons, Applicants respectfully request withdrawal of this rejection.

II. REJECTION UNDER 35 U.S.C. §102

Claims 79, 81-83 and 86-88 stand rejected under 35 U.S.C. §102 as allegedly anticipated by TaqMan® EZ RT-PCR kit. Applicants respectfully traverse this rejection.

Applicants have amended claim 79, upon which the remaining claims depend, to recite primers probes useful for amplification/detection of polynucleotides comprising SEQ ID NO:1, 2, or 5. The TaqMan EZ RT-PCR kit do not teach the probes/primers recited in claim 79. Thus, TaqMan cannot anticipate the claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

For at least the foregoing, the Applicant submits that the claimed invention is patentable and request reconsideration and notice of such allowable subject matter.

The Director is authorized to charge any required fee or credit any overpayment to Deposit Account Number 50-4586, please reference the attorney docket number above.

The Examiner is invited to contact the undersigned at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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